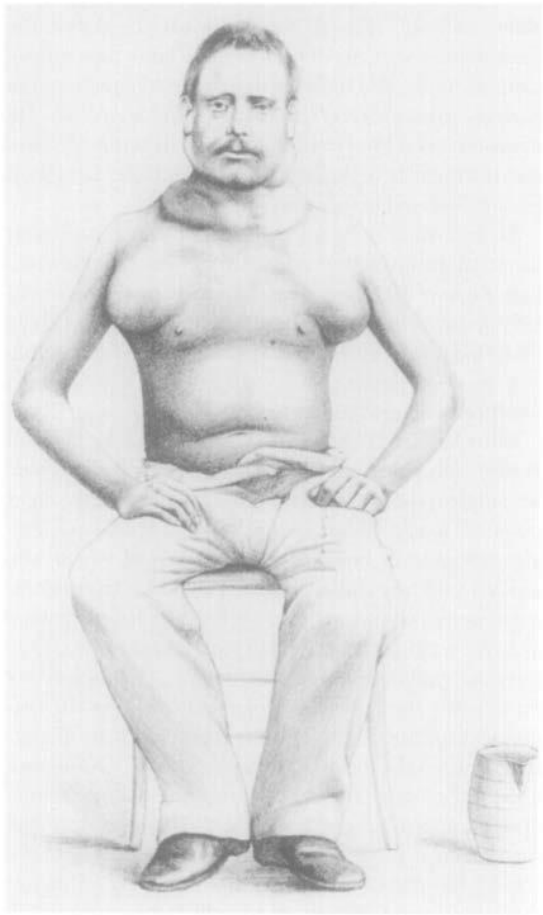
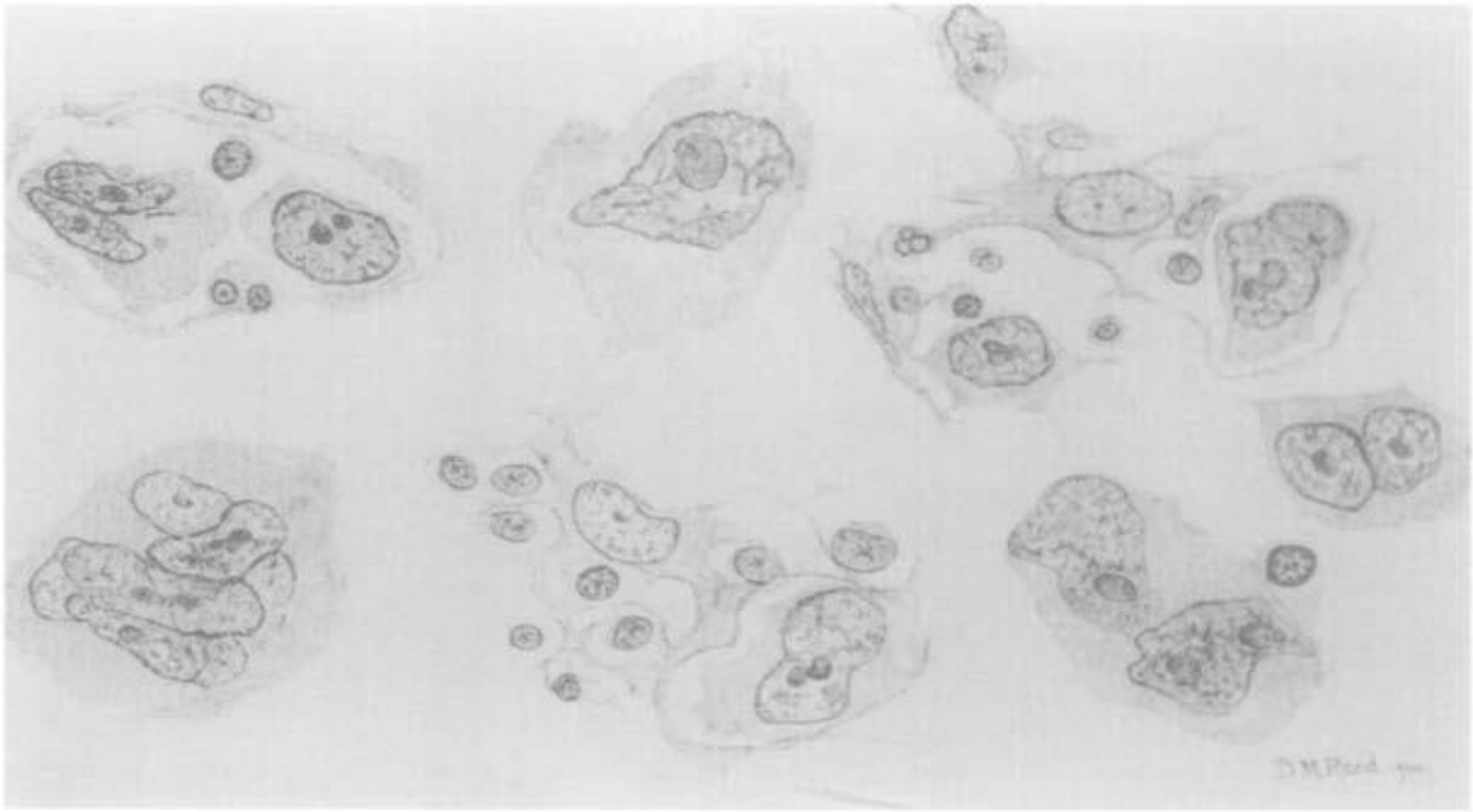
Hodgkin Lymphoma



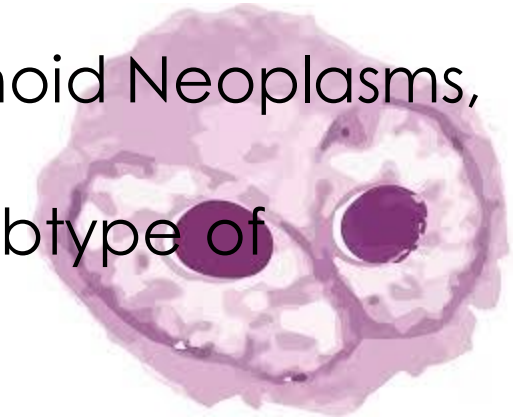


Dorothy Reed’s drawings of what came to be referred to as Reed-Sternberg cells.

In his historic 1832 paper entitled On Some Morbid Appearances of the Absorbent Glands and Spleen, Thomas Hodgkin described the clinical histories and gross postmortem findings of seven cases of the disease that was later to bear his name

Carl Sternberg and Dorothy Reed are credited with the first definitive and thorough descriptions of the pathology of cHL,

A second advance was made in 1966 when
Lukes, Butler, and Hicks proposed a classification that related well to clinical presentation and course
Their proposal was slightly modified
into the Rye classification, in which four histopathologic subtypes were described: lymphocyte-predominant, nodular sclerosis, mixed cellularity, and lymphocyte-depleted.
In the World Health Organization Classification of Lymphoid Neoplasms, the NLPHL subtype is
clearly distinguished from cHL. The “lymphocyte-rich” subtype of cHL was introduced in 1999.



POSSIBLE INFECTIOUS ETIOLOGY

Demographic features have long supported a “hygiene hypothesis” postulating that one or more subtypes of cHL represent delayed exposure to an infectious agent.

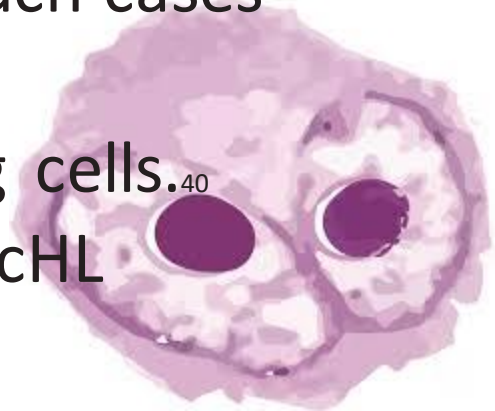
In 1966, MacMahon proposed that the first age peak in young adults was infectious in nature, whereas the second peak resulted from causes similar to other lymphomas.[26] As noted above, socioeconomic status correlates with the first, but not the second, peak.

Several reports of clustering of cHL at the time of diagnosis suggested the possibility of infectious

Transmission

A threefold increased risk of cHL in young adults is conferred by a prior history of serologically confirmed infectious mononucleosis. In addition, elevations in titers of EBV, the etiologic agent of infectious mononucleosis, have been reported in patients with cHL
EBV genomes have been detected in 30 to 50 percent of cHL tissues in developed countries, and EBV-associated cases are more common in cases with mixed cellularity histology

patients older than the age of 60 years. Several studies report a high incidence of EBV association, 85 to 100 percent, in pediatric cHL in which geographic, ethnic, and racial factors have been implicated in the
association. The incidence of cHL is 10 to 20 times higher in patients with HIV infection than in the general population, and such cases typically
have detectable EBV within Hodgkin and Reed-Sternberg cells.[40]
In contrast to non-Hodgkin lymphoma, the incidence of cHL



GENETIC BASIS

Genetic susceptibility and familial aggregation appear to play a role in the incidence of cHL.

Immunoregulatory genes within or near the major histocompatibility complex that may govern susceptibility to viral infections have been postulated to influence susceptibility to cHL, an hypothesis that is supported by the demonstration of lifelong, depressed cellular immunity in cHL patients and their healthy relatives.

Several groups described specific human leukocyte antigen (HLA) susceptibility or resistance regions, but these data have been relatively weak and sometimes inconsistent

Clinical Picture

Signs and symptoms of Hodgkin's lymphoma may include:

- Painless swelling of lymph nodes in your neck, armpits or groin
- Persistent fatigue
- Fever
- Night sweats
- Unexplained weight loss
- Severe itching
- Increased sensitivity to the effects of alcohol or pain in your lymph nodes after drinking alcohol

Paraneoplastic Findings

A number of rare paraneoplastic syndromes have been described in cHL at the time of diagnosis. These include “vanishing bile duct syndrome” and idiopathic cholangitis with clinical jaundice, the nephrotic syndrome with anasarca, autoimmune hematologic disorders (e.g., immune thrombocytopenia or hemolytic anemia), and neurologic signs and symptoms

Although parenchymal involvement of the central nervous system or meningeal involvement is rare in cHL, paraneoplastic syndromes include subacute cerebellar degeneration, myelopathy, progressive multifocal encephalopathy, and limbic encephalitis.

Localization

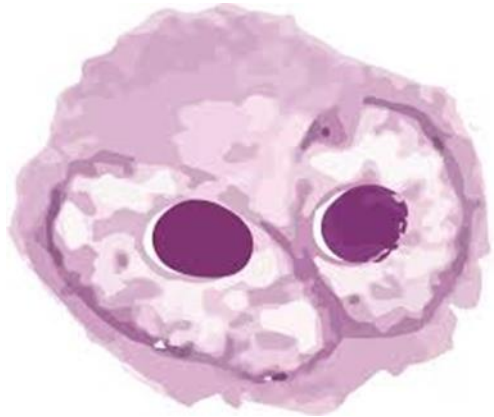
CHL most often involves lymph nodes of the cervical region (75% of cases), followed by the mediastinal, axillary, and para—aortic regions.
Non—axial lymph node groups, such as mesenteric and epitrochlear lymph nodes, are rarely involved.
Primary extranodal involvement is rare.

More than 60% of patients have localized disease (stage I or II).
Approximately 60% of patients, most with NSCHL, have mediastinal involvement.
Splenic involvement is common (20%) and is associated with an increased risk of extranodal dissemination.

Bone marrow involvement is much less common (5%). Because the bone marrow lacks lymphatics, bone marrow infiltration indicates vascular dissemination of the disease (stage IV).

Mediastinal involvement is most frequently seen in the nodular sclerosis subtype,

whereas abdominal involvement and splenic involvement are more common in mixed cellularity cases.
B symptoms consisting of fever, drenching night sweats,
and significant body weight loss are present in as many as 40% of patients.
Most patients with NLPHL are asymptomatic and present with enlargement of peripheral lymph nodes; B symptoms are rare.



Ann Arbor Staging of Lymphoma

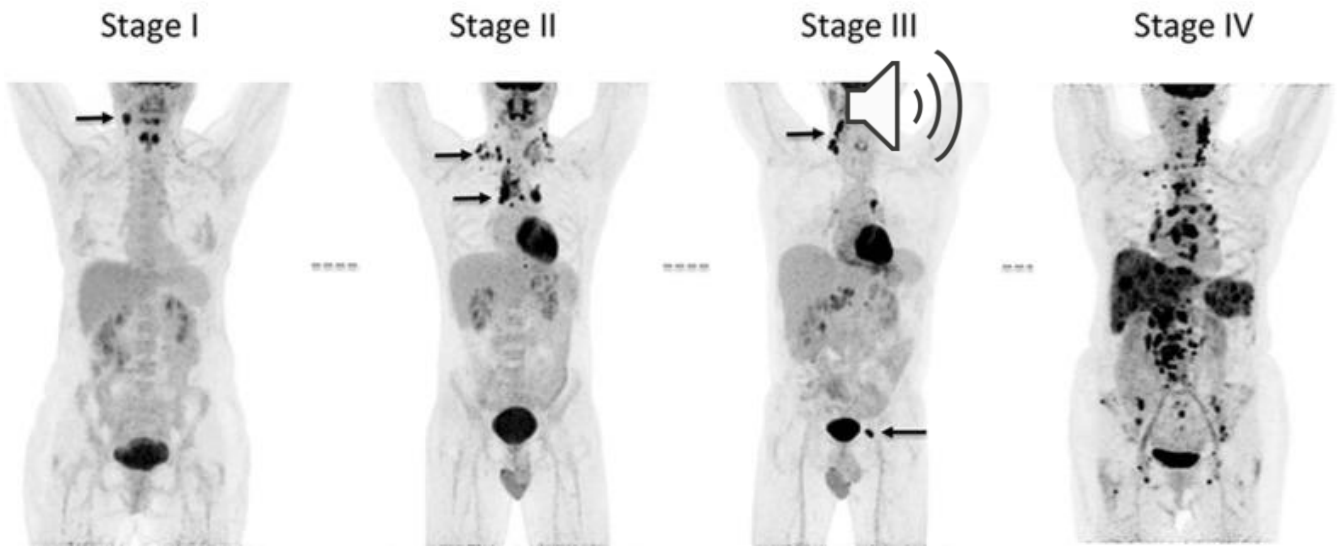


Table 32.2 Ann Arbor staging system with Cotswolds modifications.

Ann Arbor stage	Criteria
Stage I	Involvement of a single lymph node region (see Figure 32.6) or lymphoid structure*
Stage II	Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm
Stage III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Involvement of liver and bone marrow always considered stage IV
Additional classifiers	
B	Presence of B symptoms defined as • Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation • Unexplained, persistent, or recurrent fever with temperatures above 38 °C during the previous month • Recurrent drenching night sweats during the previous month
E	Limited extranodal extension from adjacent nodal site or apparent discrete single extranodal deposit (excluding liver and bone marrow)
X	A node or nodal mass greater than 10 cm (by largest dimensions of a single node or conglomerate nodal mass). Maximum width is equal to or greater than one-third of the internal transverse diameter of the thorax at the level of T5/6 on chest X-ray.

*e.g. spleen, thymus, Waldeyer's ring.

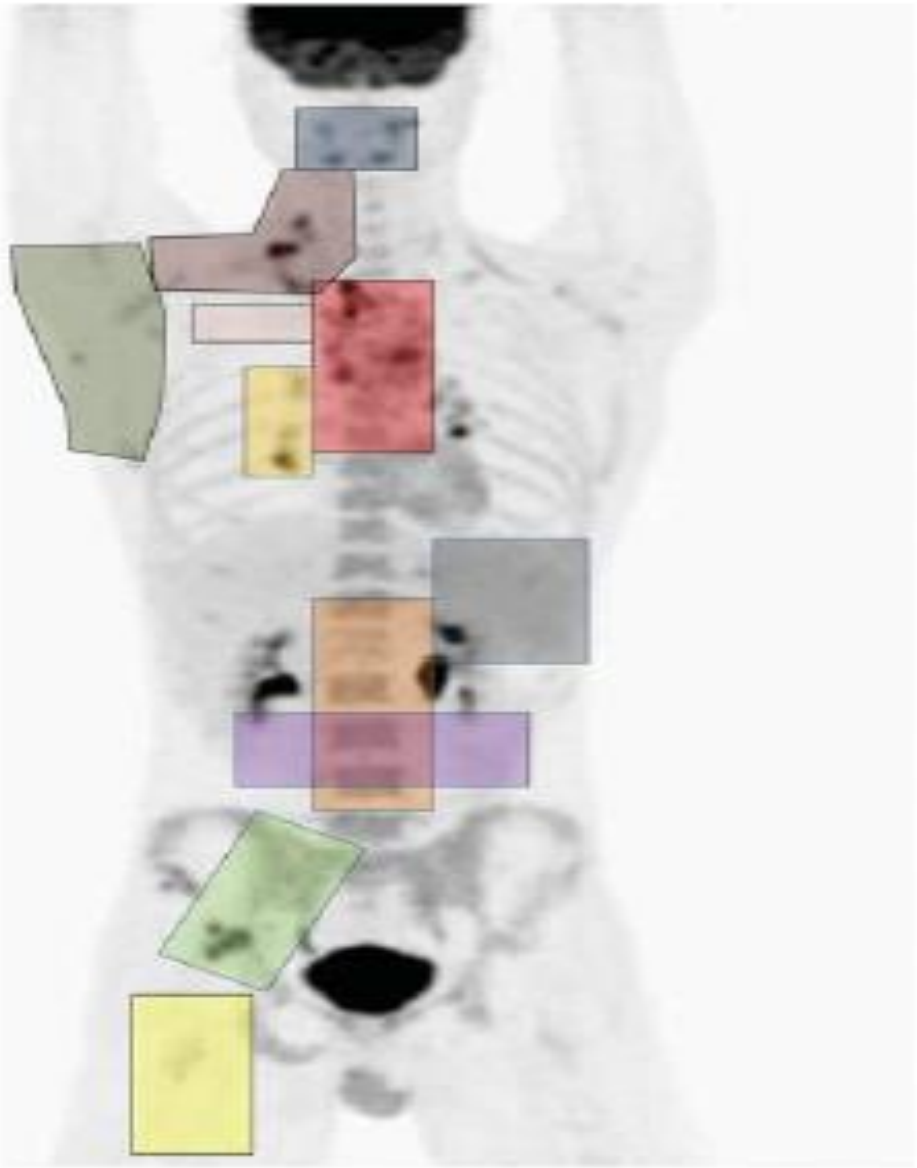


Figure 32.6
groups.

THE REED-STERNBERG CELL

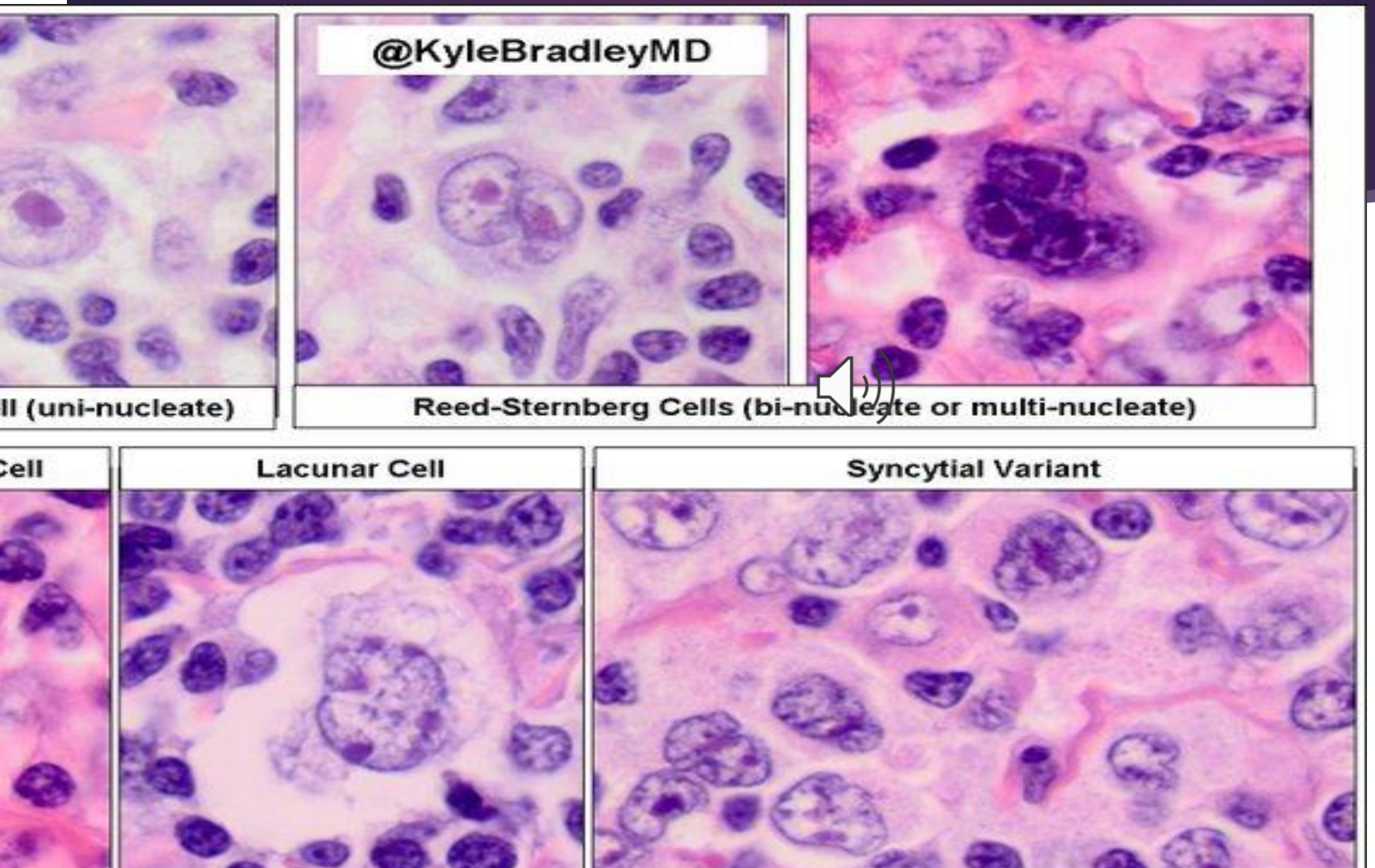
The histologic diagnosis of cHL is based on the recognition of the Reed-Sternberg cell in an appropriate cellular background. The classic Reed-Sternberg cell has a bilobed nucleus with prominent eosinophilic nucleoli separated by a clear space from the thickened nuclear membrane

Mononuclear variants
(Hodgkin cells) have similar nuclear characteristics and may represent Reed-Sternberg cells cut in a plane that shows only one lobe of the nucleus. Reed-Sternberg cells are not pathognomonic for cHL; they may be seen in reactive and other neoplastic conditions.

Typical R-S cells harbour at least two nucleoli
in two separate nuclear lobes: the so called owl's eye appearance.

Mononuclear variants are termed Hodgkin cells.
Some HRS cells may have condensed
cytoplasm and pyknotic reddish nuclei. These variants are known as mummified cells.
Many of the neoplastic cells are not prototypical Reed—Sternberg cells.

The lacunar Reed—Sternberg variant is characteristic
of nodular sclerosis CHL. The neoplastic cells typically constitute
only a minority of the cellular infiltrate,
amounting to 0.1—10%. The composition of the reactive cellular infiltrate
varies according to the histological subtype


@KyleBradleyMD
ll (uni-nucleate)
Reed-Sternberg Cells (bi-nucleate or multi-nucleate)
Cell
Lacunar Cell
Syncytial Variant

NLPHL

Clinical features

Male predominance. Patients typically presents with chronic asymptomatic peripheral lymphadenopathy. Majority present as early stage (stage I-II) disease. B-symptoms are rare. May transform to diffuse large B-cell lymphoma (DLBCL).

Lymph nodes in NLPHL may not be as reliably FDG-avid on PET scan.

Pathology

Lymph node involvement by neoplastic cells known as lymphocyte-predominant ("LP") cells which are large with folded nuclei and multiple nucleoli (also known as "popcorn" cells) in a nodular background consisting of expanded follicular dendritic cell meshworks and small B-lymphocytes.

LP cells are CD20+, CD45+, Oct-2+, BOB.1+, CD30− and CD15−.

cHL

Associated histological features
The associated cellular milieu seen in cHL is an important histological feature that helps to confirm the diagnosis of cHL (aswell as differentiating the histological subtypes). The non-malignant associated cellular component differs depending on the histological subtype as follows:

Nodular sclerosis (NS) (approx. 70–75% of cases) characterized by fibrous bands arising from a thickened capsule that run throughout the node and compartmentalize the tumour into nodules Lacunar HRS cells are typical of the NS subtype and are present within a heterogenous cellular background that consists predominantly of CD4+ T-lymphocytes, but also includes histiocytes, eosinophils, plasma cells and neutrophils

Mixed cellularity (MC) (approx. 20–25% of cases) – this subtype is named after the heterogenous inflammatory infiltrate that surrounds the HRS cells, consisting of lymphocytes, plasma cells, epithelioid histiocytes and eosinophils. Whilst there may be interstitial fibrosis in the MC subtype, broad bands of compartmentalizing fibrosis are not present.

Lymphocyte-rich (LR) (approx 5% of cases)

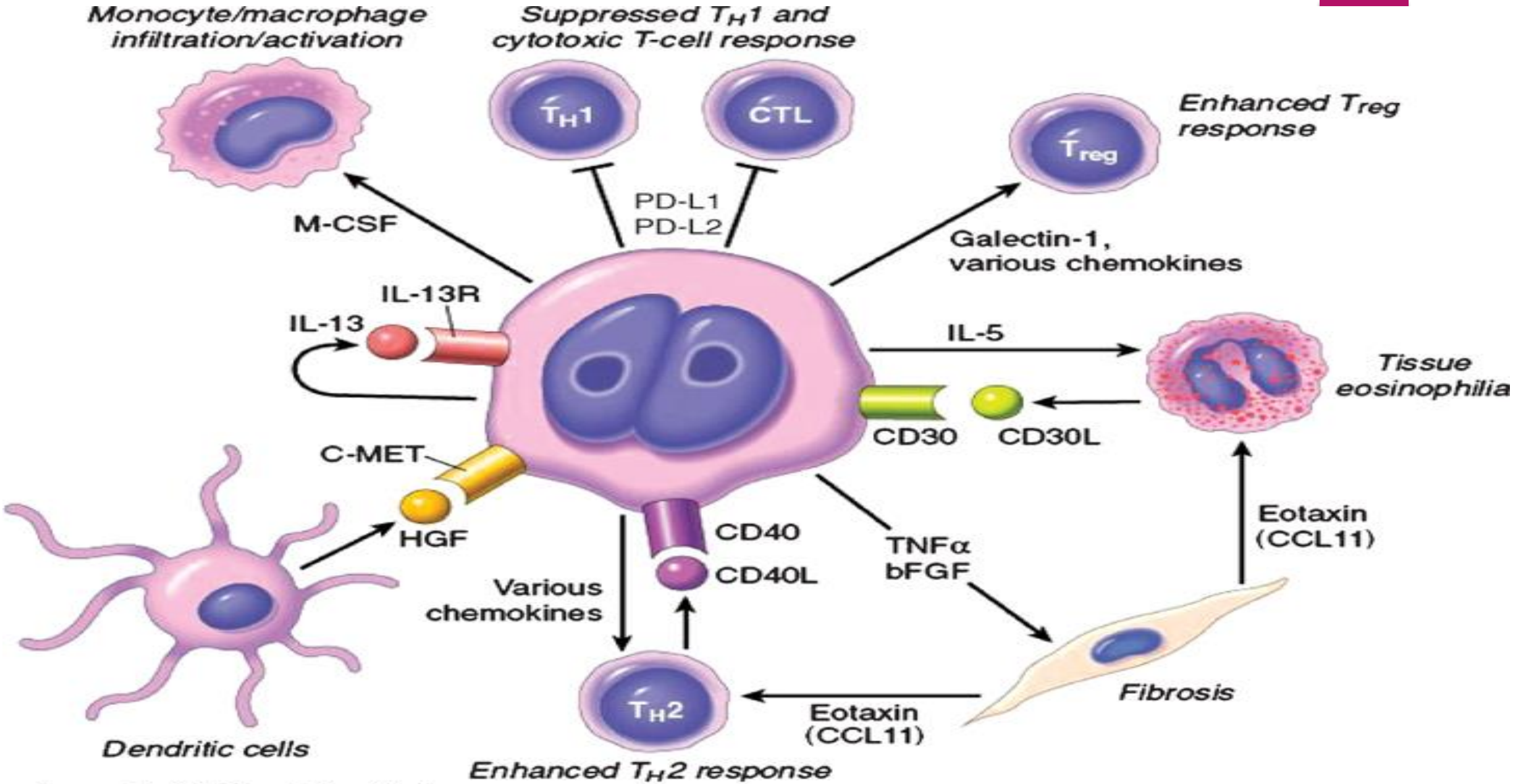
compared to the T-cell-predominant lymphocytic infiltrate in NS and MC cHL, this subtype contains a cellular background containing both B and T lymphocytes. In addition there is usually a relative paucity of neutrophils and eosinophils. This form is distinguished From NLPHL by the presence of typical HRS cells, which show membrane staining for CD30 and CD15 (which are not seen in NLPHL)

Lymphocyte-depleted (LD) (<1%of cases)

– true LD cHL is a very rare entity that histologically may be characterized by either large numbers of HRS cells or rare HRS cells in a densely fibrotic background stroma. The LD histological subtype was reported to be associated with a poorer prognosis; however, many cases were probably misclassified and included cases of ALCL.

Microenvironment

The HRS cells have a complex and symbiotic relationship with the tumour microenvironment. Numerous cytokines and chemokines are produced by HRS cells, which attract a range of immune cells including T-lymphocytes (predominantly CD4+ (TH2 and Treg)), macrophages, plasma cells and eosinophils. The cytokines and chemokines produced by HRS cells induce the surrounding inflammatory milieu to produce their own cytokines, leading to propagation of the microenvironment. The immune cells within the microenvironment in turn provide signalling to the HRS cells via surface receptors that activate intracellular pathways, including NF-κB, which contribute to the malignant phenotype of the HRS cells.



International prognostic score	5 year FFP	5 year OS
0	88%	98%
1	84%	97%
2	80%	91%
3	74%	88%
4	67%	85%
≥5	62%	67%

Score one point for each of albumin <4 g/dL, haemoglobin <105 g/L, male sex, age ≥45 years, stage IV disease, leucocytosis (≥15 × 10^9/L), lymphopenia (<8% of WCC and/or <0.6 × 10^9/L).

Immunodeficiency associated with HL

Hodgkin lymphoma—like lymphoproliferations resembling those seen in the setting of methotrexate therapy, as well as lymphoproliferative disorder with all morphological and phenotypic features of classic Hodgkin lymphoma, has been reported in patients with WAS or AT {1090,3476}. In ALPS, nodular lymphocyte predominant Hodgkin lymphoma, classic Hodgkin lymphoma, and T—cell/histiocyte—rich large B—cell lymphoma have been described {2331}.

HIV associated HL

The incidence of CHL may have increased since the introduction of cART, suggesting that a threshold of CD4+ cells may be required for the pathogenesis

In the era before cART, most cases were of the mixed—cellularity or lymphocyte—depleted subtypes. Likely due to improved immunity with anti-HIV therapy, nodular sclerosis CHL now accounts for nearly 50% of cases

HIV—associated CHL may have an atypical clinical presentation with advanced stage bone marrow or liver involvement

HC, Reed—Sternberg cells are positive for EBER in 80—100% of cases; the cells express a type II EBV latency pattern in which expression of EBV-encoded genes is limited to EBNA1 and latent membrane proteins (LMP1 and LMP2)

In HIV—related CHL, there may be decreased nodal CD4+ T cells and lack of CD4+ rosetting around Hodgkin/ Reed—Sternberg cells

Classic Hodgkin Lymphoma post—transplant lymphoproliferative disorder

Almost always EBV—positive, and should fulfil the diagnostic criteria for CHL

These lesions are usually of the mixed—cellularity type and have a type II EBV latency pattern as is typical in immunocompetent hosts.
Because Reed—Sternberg—like cells may be seen in non—destructive, polymorphic, and some monomorphic PTLDs, the diagnosis of CHL must be based on both classic morphological and immunophenotypic features, preferably including both expression of both CD15 and CD30

CD15—negative CHLs occur, caution is advised in making the diagnosis of CHL PTLD, becausethese cases must be distinguished from the other types of PTLD that include Reed—Sternberg—like cells, which are most typically EBV+, CD45+, CD15- and CD20+ and often present in association with small and intermediate—sized EBV+ lymphoid cells

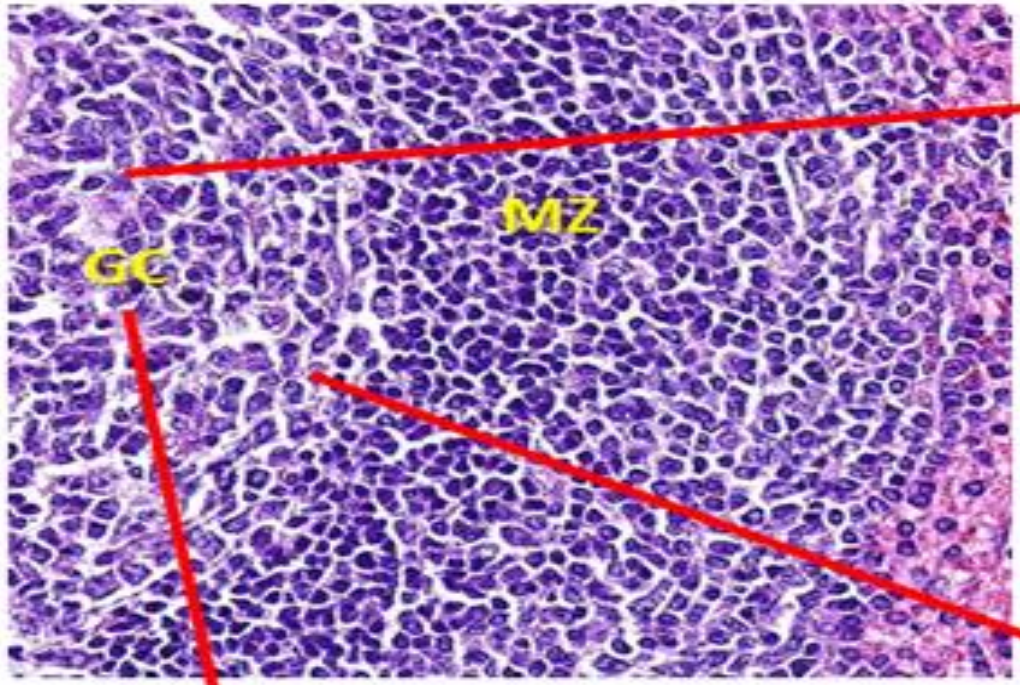
Iatrogenic ID lymphoproliferative disorders

The other iatrogenic immunodeficiency associated lymphoproliferative disorders are lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs for autoimmune disease or conditions other than in the post—transplant setting.

They constitute a spectrum ranging from polymorphic proliferations resembling polymorphic posttransplant lymphoproliferative disorders (PTLDs) to cases that fulfil the criteria for diffuse large B—cell lymphoma (DLBCL) or other B—cell lymphomas, such as EBVpositive DLBCL, peripheral T/NK—cell lymphoma, and classic Hodgkin lymphoma (CHL)

Table 15.01 Differential diagnosis of Hodgkin lymphoma: comparative tumour cell immunophenotypes

Marker	NLPHL	THRLBCL	CHL	DLBCL	ALCL, ALK+	ALCL, ALK–
CD30	– [a]	– [a]	+	–/+ [b]	+	+
CD15	–	–	+/–	–	– [c]	– [c]
CD45	+	+	–	+	+/-	+/-
CD20	+	+	–/+ [d]	+	–	–
CD79a	+	+	–/+	+	–	–
CD75	+	+	–	+	–	–
PAX5	+	+	+ [e]	+	–	–
J chain	+/–	+/–	–	-/+	–	–
Ig	+/–	+/–	– [f]	+/-	–	–
OCT2	S+	S+	–/+ [g]	+	n/a	n/a
BOB1	+	+	– [h]	+	n/a	n/a
CD3	–	–	– [a]	–	–/+	–/+
CD2	–	–	– [a]	–	–/+	+/–
Perforin / granzyme B	–	–	– [a]	–	+	+ [i]
CD43	–	–	–	–/+	+/-	+/–
EMA	+/–	+/–	– [j]	–/+ [k]	+/-	+/–
ALK	–	–	–	–	+	–
LMP1	–	–	+/–	–/+	–	–



NLPHL

LP cell phenotype:

CD30-
CD15-
MUM1+
CD20 +
B-cell transcription factors +

LRCHL

HRS cell phenotype:

CD30+
CD15+/-
MUM1+
CD20-/+
B-cell transcription factors +/-

Microenvironment:
Resembling mantle zone

cHL

HRS cell phenotype:

CD30+
CD15+
MUM1+
CD20 usually -
B-cell transcription factors usually -

Microenvironment:
Inflammatory microenvironment
and/or fibrosis

Hodgkin's Lymphoma – Management Algorithm

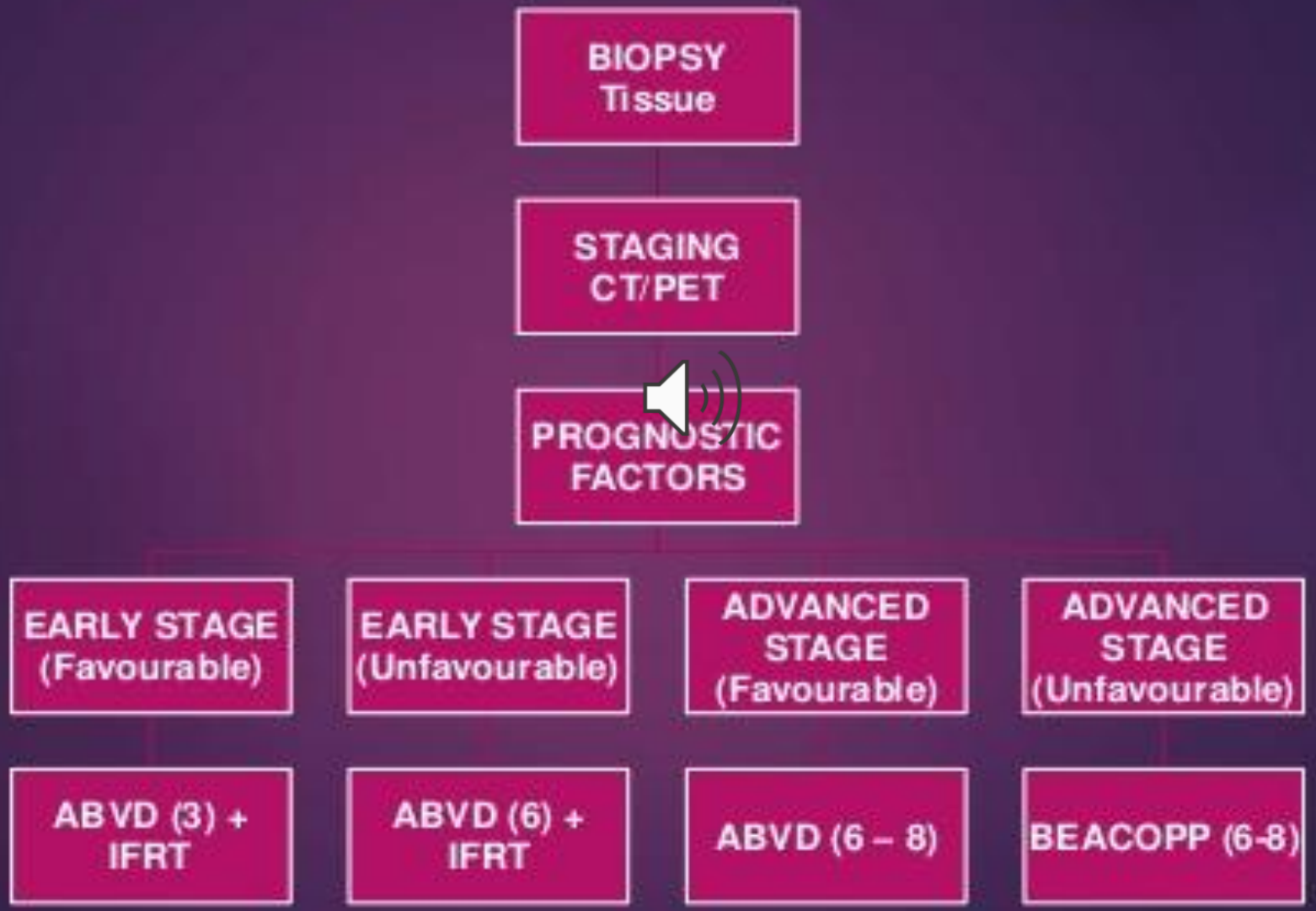
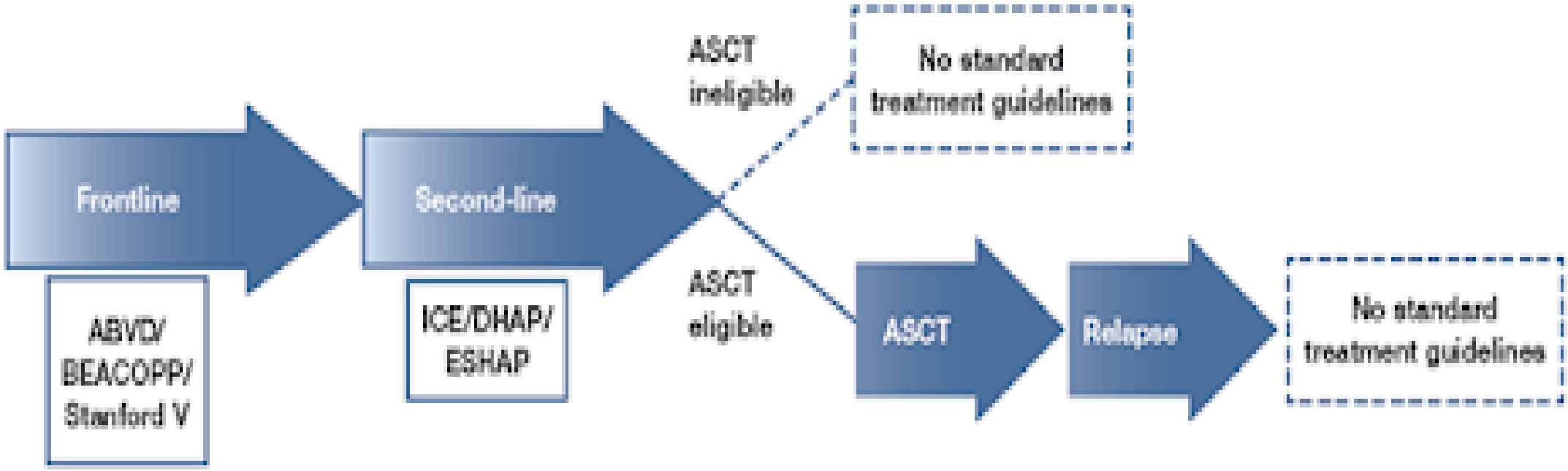


Figure 1. Typical Course of Treatment for Patients with Hodgkin Lymphoma



ABVD indicates Adriamycin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem cell transplantation; BEACOPP, bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; ICE, ifosfamide, carboplatin, etoposide; Stanford V, cyclophosphamide, Adriamycin, vincristine, procarbazine, prednisone.

Source: Reference 5.

Novel agents

One of the single most effective newanti-HL therapies to emerge is brentuximab vedotin (BV). BV is an antibody–drug conjugate, which consists of an anti-CD30 antibody conjugated to an antimicrotubule agent (monomethyl auristatin E (MMAE)). The specificity of the anti-CD30 antibody is used to guide the cytotoxin (MMAE) to the HRS cells, where binding of the anti-CD30 antibody–drug conjugate is followed by receptor mediated endocytosis and delivery of the cytotoxic agent upon hydrolysis of the linker molecule by lysosomal enzymes. Anti-CD30 antibodies that were not linked to cytotoxic agents had been investigated previously, but were found to not be effective. Other agents that have shown promise in cHL include the immunomodulatory drug lenalidomide, the histone deacetylase inhibitors (e.g. panobinostat) and the anti-PD-1 antibody nivolumab.